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What explains socioeconomic differences in the speed of heart rate recovery to postural challenge?

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ABSTRACT

Background: Much recent work has focused on the value of heart rate recovery (HRR) as a marker of cardiovascular health and a predictor of mortality. This paper explores socio-economic variation in HRR following exposure to a potent physiological stressor.

Methods: The sample involved a nationally representative cohort of 4475 community-dwelling older persons aged 50 years+ participating in the Irish Longitudinal Study on Ageing (TILDA). Participants completed an active stand (i.e. vertical stand from a supine position) as part of a detailed clinic-based cardiovascular health assessment. Beat-to-beat HRR to standing was monitored over a two-minute time horizon using a finometer. Highest level of educational achievement served as the indicator variable for socio-economic status and mediation analysis was undertaken to explore the pathways through which social inequality comes to affect the speed of HRR using the extensive array of covariates available in TILDA.

Results: Participants with primary level education were characterised by a significantly slower HRR after standing compared with the tertiary educated (B= -1.15 bpm, CI_{95} = -1.78, -0.53; $p<0.001$). Mediation analysis revealed that lifetime smoking accounted for a sizeable proportion (40.4%) of the educational differential. Adjustment for other objectively measured markers of lifestyle measured during the clinic visit accounted for only a small proportion (5.2%) of the difference.

Discussion: Smoking may represent a major pathway through which the social environment becomes biologically embedded in the tissues and organs of the body precipitating earlier vascular ageing among more socially disadvantaged groups, emphasizing the need to address the causes of these inequalities.

Keywords: socio-economic status; heart rate recovery; autonomic function; smoking; orthostasis

INTRODUCTION

Impaired heart rate recovery (HRR) following physical exertion is a marker of cardiovascular health and is associated with increased risk of cardiovascular and all-cause mortality.[1,2] HRR is usually assessed in the clinical setting by means of an exercise stress test in which the patient walks/runs on a treadmill at an intensity that is designed to stress the cardiovascular system causing an increase in heart rate (HR) and blood pressure (BP). Investigators have noted that a slower return to the baseline level of heart rate (i.e. HRR) within 1-2 minutes of the end of the exercise period is associated with older age, cardiovascular disease (CVD), and increased risk of mortality.[1] It is believed that slow HRR may signify subtle shifts in the dynamic balance of sympathetic and parasympathetic inputs to the autonomic nervous system that serve as a marker of pathophysiological disease processes that anticipate hard clinical endpoints.[3]

Despite the obvious prognostic value of HRR and the known association with CVD and mortality, few studies have examined socio-economic differences in the speed of HRR. Steptoe and colloborators[4] examined patterns of BP, HR and heart rate variability (HRV) responsiveness and recovery to two mental stress tasks across different employment grades among a subsample of participants (n=200) in the Whitehall II study. They found that post-stress recovery of BP and HRV was slower among those with low and medium employment grade ranking compared with the highest ranked group, but there were no significant differences in the speed of HRR. A separate small-scale study involving 38 men that measured Interleukin-6 concentrations and HRR following exposure to the same mental stress tasks noted that

a higher proportion of those in the high SES group (75%) had returned to baseline by 2 hours post-stress compared with only 38.1% of the low SES group.[5]

An obvious difficulty in this work is that it is not entirely clear whether the behavioural stimuli that are used to elicit the stress response are equally taxing for all social groups.[6] Tasks that involve semantic and spatial manipulation may be more challenging for individuals with lower levels of education so it is not readily apparent under these circumstances whether impaired HRR indicates dysregulation of the autonomic nervous system, as some investigators have proposed, or whether social group differences simply reflect the fact that these tasks are likely to be more difficult for someone with fewer formal years of education.

Other studies have examined socio-economic variation in HRR to a physical stressor. Shishehbor and collaborators [7] looked at the relationship of functional capacity (i.e. respiratory fitness) and HRR to all-cause mortality over a five-year follow-up period among more than 30,000 participants clinically referred for treadmill exercise. Functional capacity and HRR were found to be socio-economically patterned, and these factors accounted for 47% of the socio-economic differential in all-cause mortality in multivariable adjusted models. Carnethon and colleagues[8] measured HRR on two occasions twenty years apart in a cardiovascularly healthy cohort of people aged 18-30 years at baseline. They found that education was inversely associated with risk of incident slow HRR, even when adjusted for other demographic, metabolic and lifestyle related factors. However, neither of these studies explicitly examined the factors that contributed to SES differentials in speed of HRR.

The active stand procedure employed in the Irish Longitudinal Study on Ageing (TILDA) offers a fleeting but potentially informative two-minute time horizon for observing socio-economic variation in patterns of cardiovascular reactivity and recovery to physiological stress. The mechanics of the task are relatively simple – vertical stand from a supine position – but it is a potent cardiovascular stressor[9] and can be performed by anyone who is functionally mobile. Standing-up after a period of recumbence results in about 1/2L of central blood being translocated into the peripheral system causing a drop in blood pressure (BP) and consequent rise in HR, mediated via the autonomic nervous system and baroreceptors, to counteract the gravitational effects of standing. Peak HR is reached about 10 seconds after standing coincident with BP reaching a nadir. HR drops dramatically between 10 and 20 seconds after standing due to rebounding arterial pressure (Figure 1). McCrory and collaborators[2] have recently shown that the speed of HRR in the initial 20 seconds after standing is a strong risk marker of mortality. Specifically, they found that a one beat per minute slower HRR between 10 and 20 seconds after standing increases the hazard of all-cause mortality by 6% over a mean 4.3 year follow-up period controlling for other risk factors.

In this study we explore socio-economic variation in patterns of HRR to postural challenge. The study is novel in a number of important ways. Firstly, we document the epidemiology of HRR to standing over a two-minute time horizon among different socio-economic groups using continuous beat-to-beat monitoring of HR and BP. Secondly, we explore the extent to which a rich array of demographic, metabolic, and lifestyle-related factors are implicated in HRR to postural challenge; which may help illuminate the pathways through which socially mediated variation in exposure to

risk and protective factors over the life course becomes embedded in the tissues and organs of the body, precipitating earlier vascular disease onset and mortality among disadvantaged groups. We do this using data from a large nationally representative cohort study of ageing in the Republic of Ireland employing gold standard measures of cardiovascular functioning.

METHODS

Study Design and Participants

The Irish Longitudinal Study on Ageing (TILDA) is a large prospective cohort study examining the social, economic and health circumstances of 8,175 community-dwelling older adults aged 50 years+ resident in the Republic of Ireland. The sample was generated using a 3-stage selection process and the Irish Geodirectory as the sampling frame. A detailed description of study design is available elsewhere[10], but briefly, the study comprised 3 main components. Respondents completed a computer assisted personal interview (n=8175) in the home and a separate self-completion paper and pencil questionnaire (n=6915) that collected information on sensitive topics. All participants were subsequently invited to undergo a detailed clinical health assessment at one of two national centers using trained nursing staff. 5035 respondents attended the health centre assessment, 4891 attempted the stand, and 4475 provided valid readings. A further 114 individuals or 2.5% of those who completed the stand were missing information on at least one covariate and are excluded from the analysis resulting in a final case base of 4361 individuals.

Ethics Statement

Ethical approval for the study was obtained from the Trinity College Dublin Research Ethics Committee and signed informed consent was obtained from all participants.

Active Stand Protocol

A detailed description of the active stand protocol employed in TILDA is available elsewhere[11]. Briefly, participants who attended the health center completed an active stand from a supine position as part of a detailed cardiovascular health assessment. Participants rested comfortably in the supine position for 10 minutes prior to standing. Participants were then asked to stand in a timely manner (<5 seconds) under the supervision of a nurse and were assisted to stand if this proved necessary. Beat-to-beat variability in HR and BP during the stand were captured over a two-minute time horizon using non-invasive digital photoplethysmography (Finometer, Finapres Medical Systems, Arnhem, Netherlands). The baseline resting HR (HR_B) was calculated as the mean value of the time interval -60 to -30 seconds prior to standing. Difference from baseline measures of HRR were obtained by subtracting values of HR(t) at each time point from the baseline resting heart rate. These values are denoted $\Delta HR(t)$.

INSERT FIGURE 1 HERE

Indicator Variables for Socio-Economic Position (SEP)

Highest level of educational attainment coded as a three-level categorical variable (primary, secondary, tertiary) served as the indicator variable for SEP. These categories correspond to approximately 10, 12 and 15 years of formal education completed. Education is frequently employed as a measure of SEP because it tends to be completed early in life before the onset of many chronic conditions thereby reducing the risk of reverse causation. It is a strong determinant of future employment

and earnings[12] and captures the knowledge related assets of a person that may influence the likelihood of them engaging in health compromising behaviours (e.g. smoking) or being exposed to a range of material (e.g. poor housing), occupational (e.g. environmental toxins) or psychosocial exposures (e.g. stress) that may be detrimental to cardiovascular health.

Control Variables

We controlled in the initial model for a number of variables that were potential confounders of the relationship between SES and HRR including age, sex, pre-existing cardiovascular disease conditions, use of anti-hypertensive medications, and height. We control for sex because of sex differences in status attainment and CVD. Similarly, we control for age because of age differences in status attainment and CVD. We also controlled for measured height (cms) because it acts as a suppressor variable. That is, height is inversely correlated with the speed of HRR and positively associated with education so failure to control for it leads to an underestimate of the association between the variable of interest and the dependent variable. Medical history, including pre-existing doctor diagnosed CVDs that represent hard end-points (angina, heart attack, congestive heart failure, stroke, and transient ischemic attack) were ascertained during the household interview. Participants with atrial fibrillation were identified as such if they reported having an abnormal heart rhythm and this was confirmed from the electrocardiogram recording. These data were pooled to create a 3-level CVD disease measure: *CVD free, one CVD, two+ CVDs,* for use in the analysis. Use of anti-hypertensive medications was established by asking the respondent to retrieve the bottle/packaging of any medication they regularly take. The international non-proprietary name (INN) was assigned and coded using Anatomic Therapeutic Classification Codes (ATC). Cardiovascular medications included anti-

adrenergics (C02), diuretics (C03), beta-blockers (C07), calcium channel blockers (C08), and angiotension converting enzyme inhibitors (C09).

Putative Mediating Variables

Chronic Disease Conditions

Participants were asked during the course of the household interview whether they had ever received a doctor diagnosis of disease across a number of chronic disease categories including; cancer, lung disease and diabetes. These conditions are more common among disadvantaged groups[13-15] and represent major risk factors for cardiovascular disease. Reduced lung function increases the risk of heart failure because it diminishes the heart's capacity to pump blood effectively[16]. Autonomic dysfunction is common among those who have undergone treatment for cancer[17]; while impaired fasting glucose levels are implicated in the aetiology of autonomic dysfunction and it is believed that metabolic syndrome components precede the development of HRR rather than the reverse[18]. Responses to these questions were coded (no=0, yes=1) and they are represented as binary variables in the analysis.

Lifestyle Factors

Cigarette smoking, sedentary lifestyles, and high fat diets are leading risk factors for cardiovascular disease and are implicated in the etiology of autonomic dysfunction[19]. Lifetime smoking history was ascertained by asking respondents whether they had 'ever smoked cigarettes, cigars, cigarillos or a pipe daily for a period of at least one year?', and if so, for how many years they had smoked altogether. Cross-classification of responses to these questions produced a 5-level variable for analysis: *never smoked, past smoker<30 years*; *past smoker>=30 years*; *current smoker<30 years*; *current smoker>=30 years*. We chose a cut-off of thirty years because

smoking typically begins in early life so smoking for 30 years or more in a mid-life cohort generally indicates a lifetime smoking history[20]. Doll et al.[21] found that stopping smoking by the age of 30 eliminates almost all of the hazard of smoking, and stopping at age 50 eliminates about half the risk. Hence it seems reasonable to assume that 30 years of smoking roughly indicates the upper end of smoking risk. Respondents provided a blood sample at the health assessment and these were sent for immediate analysis to derive a detailed lipid profile which included high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides. Waist circumference, which serves as a measure of central adiposity, was measured to the nearest 0.1cm using a SECA measuring tape with the waist defined as the point midway between the iliac crest and the costal margin.

Statistical Analysis

Repeated observations of HR responses at 10 second intervals within a cross-section allows for treatment of the data as a time series (i.e. measurement occasions nested within individuals). We modeled heart rate recovery (HRR) to the stand by educational status by fitting the following model to the data which was implemented using the XTMIXED procedure in Stata.

$$y_{ij} = \alpha + \beta_j t_{ij} + \gamma X_i + \delta t_{ij} X_i + u_i + e_{ij} \qquad Eq1.$$

Where y_{ij} represents the difference in HR from baseline (ΔHR) at t_{ij}, α is the intercept, β_j is the coefficient for each time point at the reference level of each covariate, X_i represents a vector of time invariant individual-level covariates: education, age, sex, existing CVDs, use of anti-hypertensive medications, and height, and γ is the related row vector of coefficients. A cross-level interaction term between time (t_{ij} - level 1)

and individual-level covariates (X_i - level 2) is given by $t_{ij} X_i$, where δ is the related row vector of coefficients. This allows HRR to vary over time by educational status and by other covariate groups. The terms u_i and e_{ij} are residuals representing an unobserved individual effect and an error term for person *i* at time *j*, sampled from normal distributions with variances τ^2 and σ^2 respectively. The predictive margins at the means and the associated 95% confidence intervals for the cross-level time*education interaction were derived and plotted. This analysis revealed that the speed of HRR between 10 and 20 seconds after standing was the primary variable of interest – the derivation of which is described further in the results section below.

We describe the characteristics of the sample and how they vary across levels of educational attainment using survey weighted mean and standard deviations for continuous variables and the N of cases and proportions for categorical variables. The independent association of each of the covariates with the speed of HRR adjusted for age was modeled using ordinary least squares regression.

Mediation analysis was undertaken to determine the extent to which the array of mediating variables could account for the observed difference in speed of HRR between the primary and tertiary educated groups using the Karlson, Holm and Breen (KHB) method[22]. It provides a decomposition of the effects of both continuous and discrete variables, and provides analytically derived statistical tests for determining the significance of mediating variables.

The outputs from the models are interpreted as follows. The reduced model describes the estimated effect of education with no mediators in the model (i.e. total effect). The full model describes the estimated effect of education with all mediators in the model

(i.e. direct effect). The difference model is the estimated difference between these two models and represents the indirect effect. The program allows for the addition of variables to be controlled for in both the full and reduced models. The decomposition analysis shows the proportion of the total effect mediated by each of the variables. The standard error of the mediated effect can then be used to perform a statistical test of whether the putative mediating variable leads to a statistically significant change in the slope of the line relating education to speed of HRR with all other variables in the model. We tested for effect modification by fitting separate education*sex and education*age interaction terms, but as neither of the interaction terms was significant we pooled the estimates. All analyses were weighted using survey weights which incorporate both a design weight and an attrition weight to take account of non-response according to survey component (e.g. non-attendance at the health assessment). All analyses were undertaken using Stata Version 14 (Statacorp, Texas).

RESULTS

Figure 2a - 2c depicts the pattern of HRR to standing across the two minute time horizon separately for each of the educational groupings adjusting for age, sex, pre-existing cardiovascular disease burden, use of cardiovascular medications, and height (cms). All educational groups experienced a pronounced increase in HR upon standing; however the primary educated experienced a slower HRR towards baseline between 10 and 20 seconds after standing compared with the secondary and tertiary educated groups. The velocity of HRR during this time juncture is calculated by subtracting the difference from baseline value of HR at 10 seconds from the difference from baseline value of HR at 20 seconds. The primary educated experienced a mean decline in heart rate of 5.1 bpm (Fig 2a) between 10 and 20

seconds after standing compared with 6.09 for the secondary educated (Fig 2b) and 6.25 for the tertiary educated (Fig 2c). The recovery for all groups is shown simultaneously in Fig 2d.

ANOVA style tests of main effects implemented using the contrast command in Stata confirmed that the primary educated experienced a significantly slower HRR during this time window compared with the tertiary educated [B= -1.15 bpm, CI_{95}= 0.53, 1.78; p<.001]. There was no significant difference in speed of HRR at this time juncture when comparing the secondary educated with the tertiary educated [B=-0.17 bpm, CI_{95}= -0.38, 0.04]. [B=-0.17 bpm, CI_{95}= -0.38, 0.04]. Given that McCrory and collaborators[2] have previously shown that the speed of HRR during this time window predicts mortality; we employ this parameter as the unit of analysis in the present paper and use the tertiary educated as the reference category.

INSERT FIGURES 2a – 2d AS A PANEL HERE

Table 1 describes the characteristics of the sample and shows that the covariates are structured according to levels of educational attainment in a graduated manner. For example, 10.1% of those with a primary education have diabetes compared with 6.1% of those with a secondary education and 5.5% of those with a tertiary education. Similarly, 20.3% of those with a primary education are current smokers with more than 30 years of exposure compared with 15.9% and 9.9% of those with secondary and tertiary education respectively.

INSERT TABLE 1 HERE

Supplementary Table 1 shows the age adjusted association of each of the covariates with the speed of HRR in OLS regression. With the exception of cancer(s) and central adiposity (i.e. waist circumference), each of the covariates employed in the analysis was significantly associated with speed of HRR. For example, each additional year of aging was associated with a -0.31 beats per minute slower HRR. Pre-existing cardiovascular disease conditions, use of anti-hypertensive medications, taller stature, diabetes, lung disease, smoking, and elevated levels of triglycerides were associated with slower HRR to standing. By contrast, female sex, LDL and HDL were associated with faster HRR to standing.

Table 2 presents the results of the linear decomposition analysis and shows the extent to which the mediating variables explain the difference in speed of HRR between the primary and tertiary educated groups. The full multivariable regression model is presented in Supplementary Table 2. Table 2 shows that the educational differential was substantially attenuated in multivariable adjustment declining from -1.15 bpm [CI_{95}= -1.78, -0.53; p<.001] to -0.63 bpm [$CI_{95=}$ -1.20, -0.05; p<.05]. This means that 45.6% of the difference between educational groups is explained by the mediating variables. Of these, smoking was by far the most important accounting for 88.4% of the indirect effect or 40.4% of the total effect. Diabetes, cancer(s), lung disease and triglycerides accounted for the remaining 11.6% of the indirect effect or 5.2% of the total effect. Smoking was the only variable in the analysis that was a statistically significant mediator of the educational differential.

INSERT TABLE 2 HERE

DISCUSSION

In this large epidemiological study of ageing, individuals with a primary level education or equivalent were characterized by a 1.15 bpm slower HRR to postural challenge compared with those who had a tertiary level education. To place this finding in context, a previous paper has shown that a one bpm slower HRR in response to standing is associated with a 6% increase in the hazard of mortality independently of other established risk factors[2]. Parasympathetic reactivation is believed to play a key role in cardiac heart rate deceleration[23,24] so slower HRR to standing may reflect dysregulation of the autonomic nervous system and earlier ageing of the vasculature, with well-established consequences for incident CVD and mortality[3]. Given that each additional year of ageing was associated with a -0.31 bpm slower HRR, a difference of 1.15 bpm between educational groups equates to about 4 additional years of cardiovascular ageing.

That smoking accounts for 40.4% of the educational differential in the speed HRR is an important finding because smoking is a modifiable risk factor for CVD. Smoking is strongly socially patterned and individuals from lower socio-economic backgrounds are not only more likely to smoke, but they also tend to smoke at a greater intensity[25]. Lifetime smoking therefore represents a plausible pathway through which the social environment becomes biologically embedded, precipitating earlier vascular disease onset among more disadvantaged social groups. It is well established that smoking is one of the foremost risk factors for cardiovascular disease[26] and there is good evidence that smoking alters the balance of the autonomic nervous system leading to a

predominance of sympathetic nerve activity[27]. Experimental studies have shown that smoking acts on HR and increases sympathetic outflow to the heart. One study found that smokers had higher resting heart rates than non-smokers, were less likely to meet their age-predicted maximum HR during exercise; and exhibited slower HRR following the cessation of exercise[28]. Another study reported immediate benefits of smoking cessation with a decline of 7.3 beats per minute in HR following one week of abstinence[29].

As these studies strongly suggest that smoking cessation leads to immediate benefits in respiratory and cardiovascular health, it would seem that programs designed to reduce smoking among socially disadvantaged groups may help reduce inequalities in cardiovascular disease risk. Although absolute levels of smoking have declined in the developed world , the rate of decline has been greater among the more advantaged, which has served to widen socio-economic inequalities[25]. This reinforces the need for targeted interventions that reach these high risk groups. Internationally, the evidence suggests that increasing the price of cigarettes is a useful policy tool for reducing smoking amongst disadvantaged groups, and has the added benefit of deterring teenagers from initiating smoking[25]. Smoke free legislation may also help to reduce socio-economic differentials in smoking[30], but it is clear that a menu of options are required and sufficient funding/support from National Governments to address the reasons why individuals from lower socio-economic backgrounds are less successful in quitting smoking despite being equally as likely to try to quit as higher socio-economic groups[31].

Limitations

The essential criticism of this study is that it is cross-sectional so we cannot unambiguously establish the temporal relationship between the mediators and the dependent variable. We make the assumption that these variables are intermediate in the causal pathway between education and speed of HRR, but one could argue that these variables may be a consequence of slow HRR rather than a cause. In mitigation, we would argue that smoking was the only variable in the analysis that was a significant mediator of the educational differential and it seems reasonable to assume that smoking precedes slow HRR in the causal chain. Firstly, individuals who smoke tend to initiate in early life – usually during the teenage years[20]. This interpretation of the evidence is buttressed by the finding that smoking is related to speed of HRR in a dose response fashion, and that current smokers, and those who have smoked for 30 years or more are characterized by slower HRR.

Strengths

The study also has a number of strengths. This is the first large scale population based study to document the epidemiology of HRR to standing among different socio-economic groups using non-invasive methods. The active stand can be performed by anyone who is functionally mobile and is therefore a better task for examining socio-economic differences in cardiovascular reactivity to stress as it is not confounded by educational contaminants as many mental stress tasks are. The study also benefits from the strong in-depth characterization of the sample which means that we could control for a host of potential confounding variables which are not routinely captured in epidemiological studies such as cardiovascular medications, and consider a large number of candidate intermediate variables.

Conclusions

Speed of HRR is a marker of cardiovascular health and has prognostic value as a predictor of cardiovascular and all-cause mortality. The results of this study suggest that smoking is a major contributor to socio-economic differentials in cardiovascular health and reinforces the urgent need to address the factors that contribute to higher smoking rates among the more socially disadvantaged despite the well-established adverse health risks associated with smoking.

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Table 1: Baseline Characteristics of the Sample by Educational Status (n=4341)

	Primary (n=913)	Secondary (n=1830)	Tertiary (n=1598)
	Mean (SD) or N (%)	Mean (SD) or N (%)	Mean (SD) or N (%)
Control Variables			
Age (years)	66.79 (7.15)	60.79 (8.18)	60.37 (11.24)
Female sex (%)	438 (50.0)	993 (52.8)	892 (50.6)
Cardiovascular medications (%)	401 (46.4)	551 (30.2)	454 (28.1)
Cardiovascular disease status (%)			
None	762 (82.3)	1675 (91.3)	1477 (92.2)
One CVD	109 (13.1)	120 (6.8)	90 (5.9)
Two+ CVDs	42 (4.7)	35 (1.9)	31 (1.9)
Height (cms)	164.5 (7.1)	166.4 (8.9)	167.9 (12.5)
Mediating Variables			
Chronic Diseases			
Lung disease (%)	53 (6.2)	53 (3.2)	41 (2.8)
Cancer (%)	66 (7.0)	115 (6.3)	75 (4.5)
Diabetes (%)	82 (10.1)	110 (6.1)	90 (5.5)
Smoking Status			
Never smoked	354 (37.3)	842 (44.3)	802 (49.1)
Past smoker<30yrs	225 (22.7)	511 (26.8)	508 (31.4)
Past smoker>=30yrs	156 (17.1)	175 (9.4)	125 (7.8)
Current smoker<30yrs	22 (2.5)	54 (3.5)	28 (1.9)
Current smoker>=30yrs	156 (20.4)	248 (15.9)	135 (10.0)
Lipid profile			
Low density lipoprotein (mmol)	2.82 (0.74)	2.95 (0.92)	2.99 (1.30)
High density lipoprotein (mmol)	1.47 (0.31)	1.54 (0.40)	1.58 (0.63)
Triglycerides (mmol)	1.81 (0.83)	1.76 (1.07)	1.71 (1.65)
Waist circumference (cms)	97.1 (10.6)	94.9 (13.1)	93.8 (18.4)

Table 2: Difference in Speed of Heart Rate Recovery to the Active Stand and Proportion of the Total Effect Mediated by Educational Status (Primary vs Tertiary) (N=4341)

	Coef.		
Primary vs Tertiary			
Total effect (reduced model)	-1.15***		
Direct Effect (full model)	-0.63*		
Indirect Effect (difference model)	-0.52***		
% Mediated	45.6%		
Components of Difference	*Coef. (SE)*	*% of Indirect Effect*	*% of Total Effect*
Chronic Disease			
Diabetes	-0.02 (0.02)	3.93%	1.79%
Cancer	0.00 (0.01)	0.89%	0.40%
Lung disease	-0.01 (0.02)	2.20%	1.00%
Smoking Status			
Never smoked	Ref		-
Past smoker<30 years	0.01 (0.02)	-1.95%	-0.89%
Past smoker>=30 years	-0.05 (0.02)	9.82%	4.48%
Current smoker<30 years	-0.05 (0.03)	9.64%	4.40%
Current smoker>=30 years	-0.43 (0.08)	82.06%	37.43%
Lipid Profile			
Low Density Lipoprotein	0.00 (0.01)	-0.70%	-0.32%
High Density Lipoprotein	0.00 (0.03)	-0.20%	-0.09%
Triglycerides	-0.02 (0.02)	4.49%	2.05%
Waist circumference (cms)	0.05 (0.04)	-10.18%	-4.64%
TOTAL MEDIATED EFFECT	-0.52 (0.10)	100.0%	45.6%

Legend:

Reference category = tertiary educated

Total effect = Effect of education adjusted for age, sex, pre-existing CVD, use of cardiovascular medications, height (i.e. initial model)

*** Significant at the 0.001 level; ** significant at the 0.01 level; * significant at the 0.05 level

Figure 1: Mean heart rate and blood pressure response to standing averaged across 4475 participants in the Irish Longitudinal Study on Ageing (TILDA)

Legend: The haemodynamics of the cardiovascular response to standing among 4475 TILDA participants who completed the active stand is shown in Figure 1. Baseline heart rate is measured as the mean value of the time interval -60 to -30 seconds prior to standing. The participant stands at the zero time point, indicated by the vertical line on the graph. There are some anticipatory increases in HR and BP prior to standing. SBP and DBP drops quickly upon standing reaching a nadir at about 10 seconds and recovering quickly towards baseline between 10 and 20 seconds. HR increases rapidly in the first 10 seconds to counteract the gravitational forces acting on BP, peaks at about 10 seconds and declines rapidly between 10 and 20 seconds.

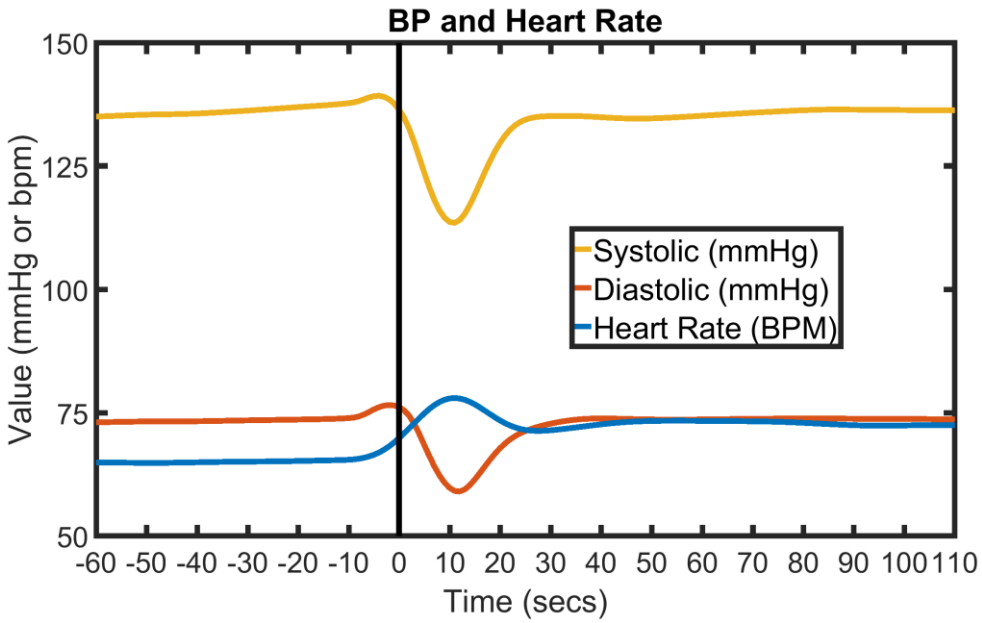


Figure 2: Speed of Heart Rate Recovery in Beats per Minute in Response to Postural Challenge by Highest Level of Educational Attainment

Legend**:** The haemodynamics of the heart rate response to standing over the two-minute time horizon is presented separately for each of the educational groupings: primary (Fig. 2a), secondary (Fig. 2b), and tertiary (Fig. 2c). The estimates were derived controlling for age, sex, existing cardiovascular disease burden, use of cardiovascular medications, and height. There was a social gradient in the speed of heart rate recovery towards baseline between 10 and 20 seconds after standing. The tertiary educated experienced the most pronounced drop in heart rate during this time period which is considered a marker of cardiovascular health and vitality. Figure 2d shows the relationships for all educational groups simultaneously. Note that the speed of heart rate recovery between 10-20 seconds is the time point where the difference between educational groups is most pronounced. Error bars represent the 95% confidence intervals.

Fig. 2a

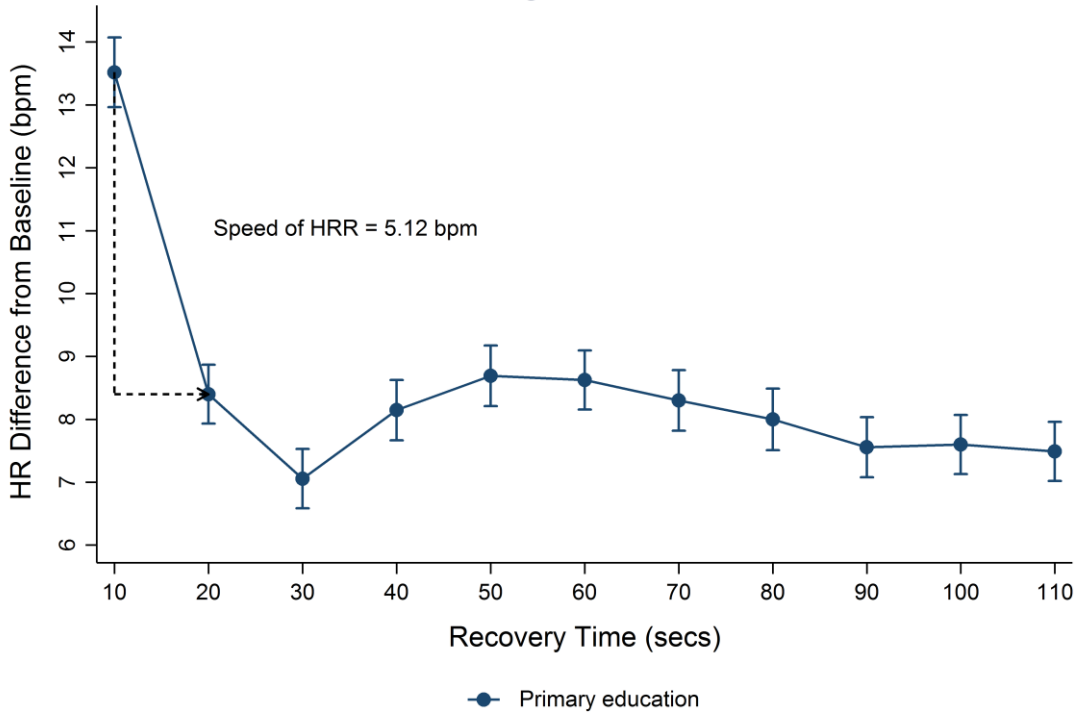

HR Difference from Baseline (bpm)
6
7
8
9
10
11
12
13
14
Speed of HRR = 5.12 bpm
10
20
30
40
50
60
70
80
90
100
110
Recovery Time (secs)
Primary education

Fig. 2b

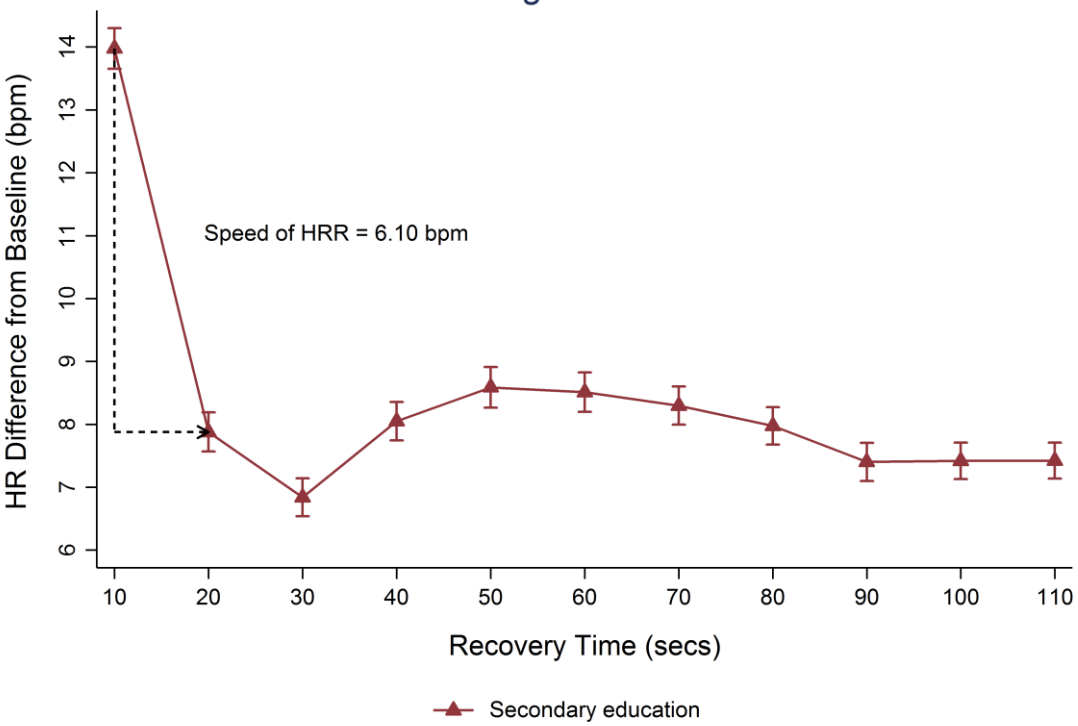

HR Difference from Baseline (bpm)
6
7
8
9
10
11
12
13
14
Speed of HRR = 6.10 bpm
10
20
30
40
50
60
70
80
90
100
110
Recovery Time (secs)
Secondary education

Fig. 2c

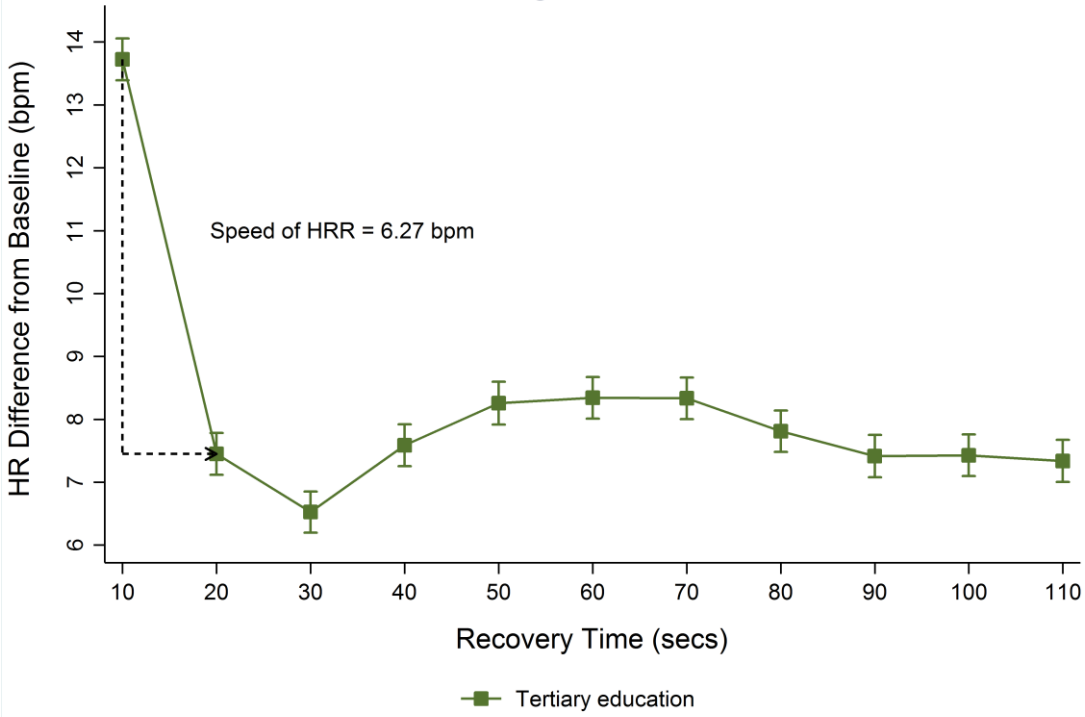
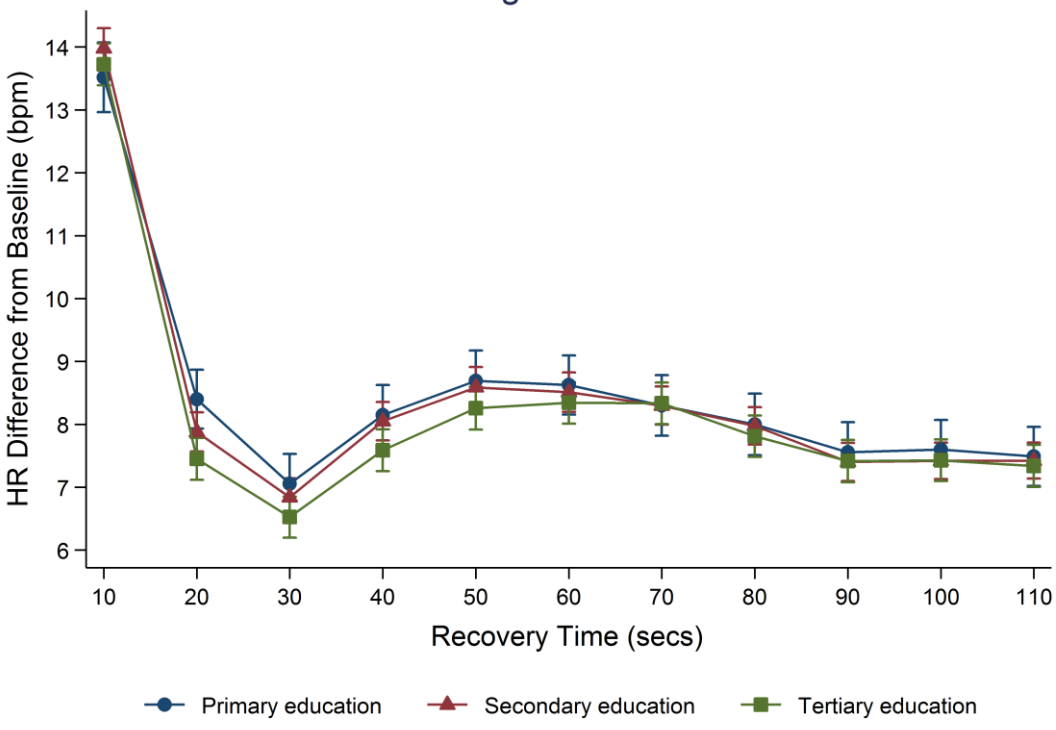

HR Difference from Baseline (bpm)
6
7
8
9
10
11
12
13
14
Speed of HRR = 6.27 bpm
10
20
30
40
50
60
70
80
90
100
110
Recovery Time (secs)
Tertiary education

Fig. 2d


HR Difference from Baseline (bpm)
6
7
8
9
10
11
12
13
14
10
20
30
40
50
60
70
80
90
100
110
Recovery Time (secs)
Primary education
Secondary education
Tertiary education

Socioeconomic Differences in the Speed of Heart Rate Recovery to Postural Challenge

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Supplementary Table 1: Age adjusted association of each of the covariates with speed of Heart Rate Recovery (HRR) in ordinary least squares regression (n=4341)

	B (95% CI)	*p-value*
Control Variables		
Age (years)	-0.31 [-0.28, -0.33]	<.001
Female gender	0.52 [0.07, 0.96]	<.05
Cardiovascular medications	-1.66 [-2.19, -1.13]	<.001
Cardiovascular disease status		
CVD free	Ref	-
One CVD	-1.44 [-2.38, -0.51]	<.01
Two+ CVDs	-2.80 [-4.16, -1.44]	<.001
Height (cms)	-0.06 [-0.09, -0.04]	<.001
Mediating Variables		
Diabetes	-1.89 [-2.79, -1.00]	<.001
Cancer(s)	-0.62 [-1.48, 0.24]	n.s
Lung disease	-1.43 [-2.79, -0.08]	<.05
Smoking History		
Never smoked	Ref	-
Past smoker<30 years	-0.32 [-0.85, 0.22]	n.s
Past smoker>=30 years	-1.66 [-2.42, -0.90]	<.001
Current smoker<30 years	-2.99 [-4.56, -1.42]	<.001
Current smoker>=30 years	-3.16 [-3.98, -2.33]	<.001
Lipid Profile		
Low density lipoprotein	0.53 [0.26, 0.80]	<.001
High density lipoprotein	0.85 [0.31, 1.38]	<.01
Triglycerides	-0.29 [-0.52, -0.06]	<.05
Waist circumference (cms)	-0.02 [-0.03, 0.00]	n.s

Legend: A negative coefficient signifies that the variable is associated with slower HRR.
Ref = reference category

Supplementary Table 2: Crude and Multivariable Adjusted Association of the Covariates with Speed of Heart Rate Recovery (HRR) in Ordinary Least Squares Regression (n=4341)

	Crude		*Multivariable*	
	Coef.	*[95% CI]*	*Coef.*	*[95% CI]*
Educational Status				
Primary	-1.15***	[-1.78, -0.52]	-0.63*	[-1.22, -0.03]
Secondary			0.07	[-0.36, 0.50]
Tertiary			REF	-
Age (years)			-0.29***	[-0.33, -0.26]
Female sex			-1.39***	[-2.04, -0.74]
Anti-hypertensive medications			-1.30***	[-1.84, -0.76]
Cardiovascular Disease Status				
None			REF	-
One CVD			-0.54	[-1.45, 0.37]
Two+ CVDs			-1.59*	[-2.99, -0.19]
Height (cms)			-0.13***	[-0.17, -0.09]
Chronic Disease				
Diabetes			-1.22**	[-2.13, -0.31]
Cancer			-0.45	]-1.24, 0.33]
Lung Disease			-0.39	[-1.60, 0.81]
Smoking History				
Never smoked			REF	-
Past smoker <30 years			-0.14	[-0.67, 0.40]
Past smoker>30 years			-1.21**	[-1.99, -0.44]
Current smoker<30 years			-2.90***	[-4.43, -1.37]
Current smoker>30 years			-3.07***	[-3.88, -2.25]
Lipid profile				
low density lipoprotein			0.32*	[0.06, 0.57]
high density lipoprotein			-0.01	[-0.55, 0.53]
triglycerides			-0.17	[-0.40, 0.06]
Waist circumference			0.02	[0.00, 0.04]
CONSTANT			45.91	[38.63, 53.18]

*** Significant at the 0.001 level; ** significant at the 0.01 level; * significant at the 0.05 level

Ref = reference category